REMARKS

This Reply is responsive to the Office Action dated April 8, 2004. Entry of the amendments and remarks submitted herein and reconsideration of the claimed subject matter pursuant to 37 CFR §1.112 is respectfully requested.

I. Status of the Claims

Claims 1-14 were pending in this application at the time of the Office Action dated June 3, 2003. Claims 8 and 10-13 were withdrawn from consideration. Accordingly, claims 1-7, 9 and 14 are now under examination.

II. Amendments to the Claims

Claim 1 has been amended above to delete unnecessary language, and to rephrase the claim language to emphasize that according to the claimed method, the antibodies are produced in a cellular compartment of a plant. Dependent claims have been amended accordingly. No prohibited new matter has been added by way of these amendments.

III. Prior Art Rejections

Claims 1, 3, 7, 9 and 14 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Magnuson *et al.* According to the Office Action, Magnuson *et al.* teach a method for modifying a plant to produce a heavy chain immunoglobulin devoid of a variable light chain domain in the cytoplasm and cell membrane. Applicants respectfully traverse the rejection.

Magnuson discloses the recovery of secreted mouse monoclonal antibody heavy chain gamma (Mab HC) from cell suspension cultures of genetically modified tobacco cells. The present claims are directed to methods for modifying a plant to produce a heavy chain immunoglobulin devoid of variable light chain (VHH) in a cellular compartment of the plant. Magnuson provides a teaching which is only directed to plant cell suspensions. The successful excretion of monoclonal antibody heavy chains in a tobacco cell suspension is not the same as the production of VHH in plant cellular compartments. Further, the cell suspension culture and conditions of culturing disclosed in Magnuson *et al.* would not teach one how to achieve production of a VHH in a plant cellular compartment because cell suspension conditions are very different from growth conditions in an actual plant.

Because Magnuson *et al.* does not teach production of heavy chain immunoglobulins in a cellular compartment of a plant, Magnuson *et al.* does not anticipate any of the present claims under §102(b). Accordingly, reconsideration and withdrawal of the rejection based on Magnuson *et al.* are respectfully requested.

Claims 1, 2, 7, 9 and 14 were rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Casterman *et al.* This rejection is based on the general reference in Casterman to Hiatt *et al.* as disclosing specific promoters and signal peptides for expression in plants, since Casterman does not disclose the actual production of the disclosed heavy chain antibodies in plants. Applicants respectfully maintain their traversal.

In the reply filed December 3, 2003, Applicants noted that a mere reference to another article that teaches bits and pieces of items required to practice the claimed

invention does not translate to an enabling disclosure for the cited reference. Indeed, according to MPEP 2131.01, extra references may be relied upon to show a primary reference contains an "enabled disclosure" when the claimed composition or machine is disclosed *identically* by the reference. *In re Samour*, 571 F.2d 559 (CCPA 1978), and *In re Donahue*, 766 F.2d 531 (Fed. Cir. 1985) (with emphasis). Applicants further noted that a reference that merely postulates that something *could* be done does not *identically* disclose the invention. Indeed, if attempts at performing the invention were unsuccessful before the date of invention, then a reference that merely suggests that something could be done, but does not actually put it into practice, does not contain an enabling disclosure.

According to the Office Action, the Casterman reference is enabled because the Hiatt reference cited in Casterman "would in fact anticipate the rejected claims but for the requirement of claim 2 that the heavy chain immunoglobulin be obtained from camelids, and but for the silence of Hiatt *et al.* with respect to whether their expressed heavy chain immunoglobulin is capable of specific binding with an antigen" (with emphasis). Applicants respectfully submit that the "but for" clauses included in the Office Action support Applicants' position. It is clear that neither Casterman *et al.* nor Hiatt *et al.* teach all the limitations of the claimed invention, therefore, neither of these references is prior art under §102.

The mere fact that Casterman *et al.* mentions Hiatt *et al.* does not mean that Casterman *et al.* has put into practice the production of heavy chain antibodies in plants. Hiatt *et al.* concerns the assembly of kappa and gamma chains in plants to form a functional complete murine antibody comprising a heavy and a light chain. Hiatt does not disclose the production of heavy chain only immunoglobulins in plants. In fact, as

discussed in the Background of the present specification, several groups have reported the functional expression of murine monoclonal antibodies in plants, including During *et al.* (1990) and Ma *et al.* (1994) (see specification, p. 2). Therefore, as acknowledged in the Background of the specification, it might have been expected at the time that expression of smaller antibody fragments, with their less stringent assembly requirements, could also be performed in plants. This was not the case, however, as it had been reported in practice that better yields are achieved with plants transformed with complete murine antibodies rather than small fragments (Ma *et al.*, Science, 268: 716-19 (1995)) (see paragraph bridging pp. 2-3 of specification).

Indeed, as observed by Hiatt *et al.*, "the yield of each chain is increased in plants expressing both gamma and kappa, indicating that assembly of the gamma-kappa complex might enhance stability" (p. 77, col. 2). The skilled artisan having read this passage would be led away from applying the methods of Hiatt *et al.* to the production of heavy chain antibodies in plants, particularly in view of the difficulties known in the art in expressing functional heavy chain fragments in plants. A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983). It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).

The Office Action asserts that Applicants' arguments concerning evidence of unpredictability in the art is not germane to the instant rejection, since the claims are rejected as being anticipated under §102 rather than as obvious under §103, and "since

Hiatt *et al.* in fact successfully introduced into a plant and expressed a DNA sequence encoding a heavy chain immunoglobulin devoid of a variable light chain domain" (Office Action, p. 4). Applicants respectfully note that there is no indication in Hiatt *et al.* that the small amount of heavy chain actually produced in the absence of light chain is functional. Moreover, evidence of unpredictability in the art is indeed germane to the instant rejection, since it appears that the Examiner, in principle, has made an obviousness rejection by combining Casterman *et al.* and Hiatt *et al.* Again, neither of these references teaches how to put the claimed invention into practice. Furthermore, Hiatt *et al.* actually teaches away from the production of heavy chain only immunoglobulins, since the reference discloses that the heavy chain expressed alone appears to be significantly less stable than when coexpressed with light chain.

For all the reasons discussed above, Applicants respectfully submit that Casterman *et al.* is not prior art under §102(b) or §103. Casterman *et al.* does not teach all the limitations of the claimed invention, since Casterman *et al.* merely suggests that the disclosed heavy chain antibodies might be produced in plants. Reference to Hiatt *et al.* does not make Casterman *et al.* enabled for the claimed invention, given that Hiatt *et al.* actually teaches away from expressing heavy chain only immunoglobulins in plants. Reconsideration and withdrawal of the rejection based on Casterman *et al.* is respectfully requested.

Claim 4 was rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over either Magnuson *et al.* or Casterman *et al.* in view of Owen *et al.* The Office Action acknowledges that neither Magnuson nor Casterman teach the expression in plants of a DNA sequence encoding a heavy chain immunoglobulin devoid of a variable light chain

but capable of specific binding with an antigen that is a protein present in a plant. However, according to the Office Action, it would be obvious to express such a heavy chain antibody in plants, given the success of Magnuson *et al.* and Casterman *et al.* in expressing heavy chain immunoglobulins in plants, and given the success of Owen *et al.* of expressing in a plant a single chain Fv fragment capable of binding a plant antigen. Applicants respectfully traverse the rejection.

As explained above Magnuson *et al.* teach expression of heavy chain immunoglobulin in a cell suspension culture. This does not represent production in compartments of a real plant. The conditions of growth in a cell suspension culture are much more controlled and easily optimised for protein production. The expression in a compartment of a plant is more difficult and subject to more complex processes. Therefore the mere expression in a cell suspension is not the same as the successful production of VHH in plant cellular compartments.

Although Casterman *et al.* mention that the disclosed VHH may be produced in plants, this was a mere invitation to experiment and not an enabling disclosure of the production of a VHH in a plant cellular compartment. Again, as discussed at length above and incorporated herein for convenience, the mere reference to the plant promoters disclosed in Hiatt *et al.* does not provide an enabling disclosure, particularly given that Hiatt *et al.* teaches away from the production of heavy chain only immunoglobulins in plants, and further given the state of the art at the time.

Owen *et al.* does not make up for the deficiencies of Magnuson *et al.* and Casterman *et al.*, since Owen *et al.* also provide no disclosure of heavy chain only antibodies in plants. Accordingly, the fact that the single chain Fv fragments disclosed in

Owen were able to bind to a plant antigen would not render the claimed invention obvious. Reconsideration and withdrawal of the rejection under §103(a) based on Magnuson *et al.* or Casterman *et al.* and Owen *et al.* are respectfully requested.

Claim 5 was rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over either Magnuson *et al.* or Casterman *et al.* in view of Le Gall *et al.* The Office Action acknowledges that neither Magnuson nor Casterman teach the expression in plants of a DNA sequence encoding a heavy chain immunoglobulin devoid of a variable light chain but capable of specific binding with an antigen that is a pathogen present in a plant. However, according to the Office Action, it would be obvious to express such a heavy chain antibody in plants, given the success of Magnuson *et al.* and Casterman *et al.* in expressing heavy chain immunoglobulins in plants, and given the success of Le Gall *et al.* of expressing in a plant a single chain Fv fragment capable of binding a plant antigen that is a stolbur phytoplasma plant pathogen. Applicants respectfully traverse the rejection.

As explained above with reference to the rejection of claim 4, Magnuson *et al.* teach expression of heavy chain immunoglobulin in a cell suspension culture. This does not represent production in compartments of a real plant as recited in the present claims. Although Casterman *et al.* mention that the disclosed VHH may be produced in plants, this was a mere invitation to experiment and not an enabling disclosure of the production of a VHH in a plant cellular compartment. LeGall *et al.* does not make up for the deficiencies of Magnuson *et al.* and Casterman *et al.*, since Le Gall *et al.* also provide no disclosure of heavy chain only antibodies in plants. Accordingly, the fact that the single chain Fv fragments disclosed in Le Gall were able to bind to a plant pathogen would not

render the claimed invention obvious. Reconsideration and withdrawal of the rejection under §103(a) based on Magnuson *et al.* or Casterman *et al.* and Le Gall *et al.* are respectfully requested.

Claim 6 was rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over either Magnuson *et al.* or Casterman *et al.* in view of Artsaenko *et al.* The Office Action acknowledges that neither Magnuson nor Casterman teach the expression in plants of a DNA sequence encoding a heavy chain immunoglobulin devoid of a variable light chain but capable of specific binding with an antigen that is a plant hormone or metabolite. However, according to the Office Action, it would be obvious to express such a heavy chain antibody in plants, given the success of Magnuson *et al.* and Casterman *et al.* in expressing heavy chain immunoglobulins in plants, and given the success of Artsaenko *et al.* of expressing in a plant a single chain Fv fragment capable of binding an abscisic acid plant hormone. Applicants respectfully traverse the rejection.

As explained above with reference to the rejections of claims 4 and 5, Magnuson *et al.* teach expression of heavy chain immunoglobulin in a cell suspension culture. This does not represent production in compartments of a real plant as recited in the present claims. Although Casterman *et al.* mention that the disclosed VHH may be produced in plants, this was a mere invitation to experiment and not an enabling disclosure of the production of a VHH in a plant cellular compartment. Artsaenko *et al.* does not make up for the deficiencies of Magnuson *et al.* and Casterman *et al.*, since Artsaenko *et al.* also provide no disclosure of heavy chain only antibodies in plants. Accordingly, the fact that the single chain Fv fragments disclosed in Artsaenko were able to bind to a plant pathogen would not render the claimed invention obvious. Reconsideration and

withdrawal of the rejection under §103(a) based on Magnuson *et al.* or Casterman *et al.* and Artsaenko *et al.* are respectfully requested.

This reply is fully responsive to the Office Action dated April 8, 2004. Therefore, a Notice of Allowance is next in order and is respectfully requested.

Except for issue fees payable under 37 CFR §1.18, the commissioner is hereby authorized by this paper to charge any additional fees during the pendency of this application including fees due under 37 CFR §1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 CFR §1.136(a)(3).

If the Examiner has any further questions relating to this Reply or to the application in general, she is respectfully requested to contact the undersigned by telephone so that allowance of the present application may be expedited.

Respectfully submitted
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